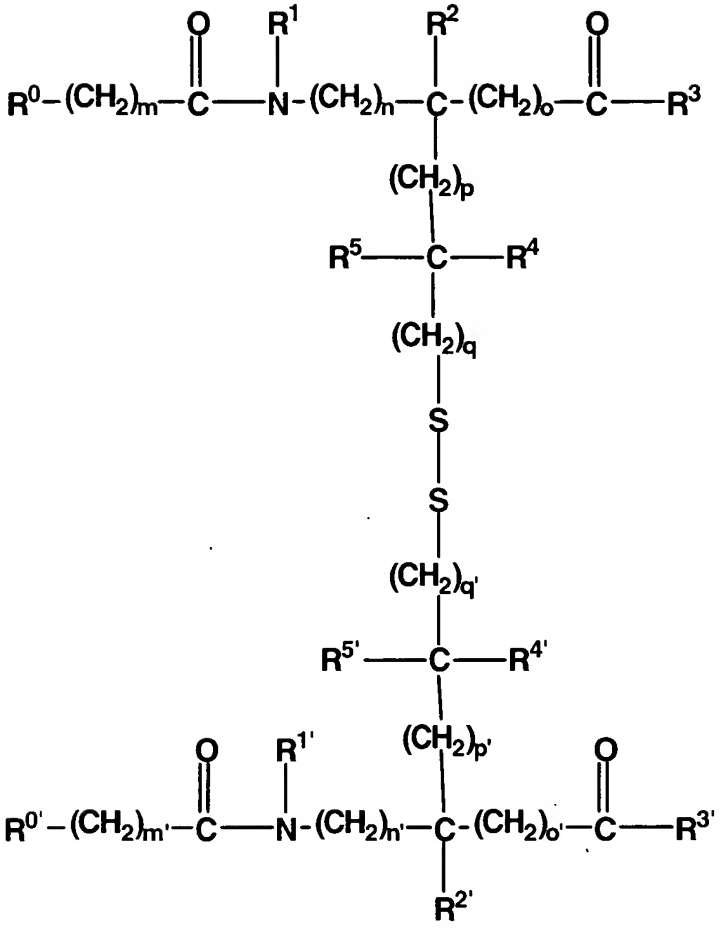
CLAIMS

What is claimed is:

1. A method for treating, preventing and/or reducing inflammation, pain, and fever; for decreasing or reversing the gastrointestinal, renal and other toxicities resulting from the use of nonsteroidal antiinflammatory compounds; for treating and/or preventing gastrointestinal disorders; for facilitating wound healing; for treating inflammatory disease states and/or disorders; for treating and/or preventing ophthalmic diseases and/or disorders; for treating and/or improving gastrointestinal properties of COX-2 selective inhibitors; for treating and/or preventing renal toxicity; for treating and/or preventing COX-2 mediated disorders; for decreasing the recurrence of ulcers; for improving gastroprotective properties, anti-*Helicobacter pylori* properties or antacid properties of proton pump inhibitors; for treating and/or preventing bacterial infections, microbial infections, multiple sclerosis, and/or viral infections; for improving gastroprotective properties of H_2 receptor antagonists; for treating and/or preventing restenosis, autoimmune diseases, pathological conditions resulting from abnormal cell proliferation, polycystic kidney disease, inflammatory diseases or to inhibit wound contraction; for treating or preventing sexual dysfunctions in males and females, for enhancing sexual responses in males and females; for treating or preventing benign prostatic hyperplasia, hypertension, neurodegenerative disorders, vasospastic diseases, cognitive disorders, urge incontinence, or an overactive bladder; for reversing the state of anesthesia; for treating or preventing diseases induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate (cGMP) or for treating respiratory disorders, in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one compound of Formula I or II, or a pharmaceutically acceptable salts thereof,

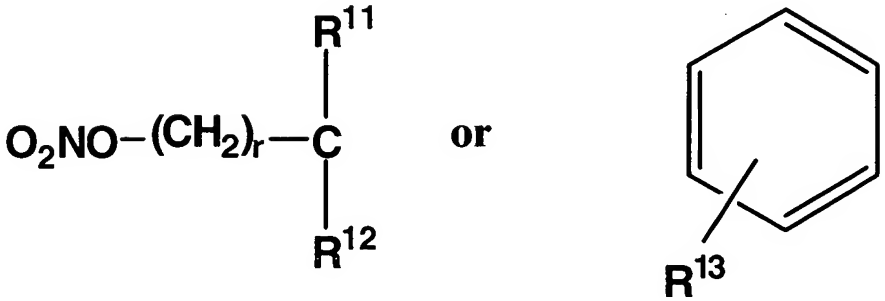
wherein the compound of Formula (I) is:



(I)

wherein:

R^0 and $R^{0'}$ are:



R^{11} is hydrogen, an alkyl group having 1 to 6 carbon atoms, a substituted lower alkyl wherein the substituent is halogen, hydroxyl, lower alkoxy, aryloxy, amino, lower alkylamino, acylamino, acyloxy, arylamino, mercapto, lower alkylthio or arylthio,

R^{12} is R^{11} hydrogen or a lower alkyl group;

R^{13} is a nitratoalkyl group having 1 to 6 carbon atoms;

r is an integer from 0 to 10;

R^1 and $R^{1'}$ are each independently hydrogen or lower alkyl;

R^2 and $R^{2'}$ are each independently hydrogen, lower alkyl, phenyl, methoxyphenyl, phenyl-lower-alkyl, methoxyphenyl-lower-alkyl, hydroxyphenyl-lower-alkyl, hydroxy-lower-alkyl, alkoxy-lower-alkyl, amino-lower-alkyl, acylamino-lower-alkyl, mercapto-lower-alkyl or lower alkylthio-lower-alkyl;

R^3 and $R^{3'}$ are each independently hydroxyl, lower alkoxy, lower alkenoxy, di-lower-alkylamino-lower-alkoxy, acylamino-lower-alkoxy, acyloxy-lower-alkoxy, aryloxy, aryl-lower-alkoxy, substituted aryloxy or substituted aryl-lower-alkoxy, in which the substituent is methyl, halogen or methoxy; amino, lower alkylamino, di-lower-alkylamino, aryl-lower-alkylamino, hydroxy-lower-alkyl-amino, pyrrolidine, piperidine, morpholine, piperazine or amino-acid residues via peptide linkage;

R^4 and $R^{4'}$ are each independently hydrogen or lower alkyl;

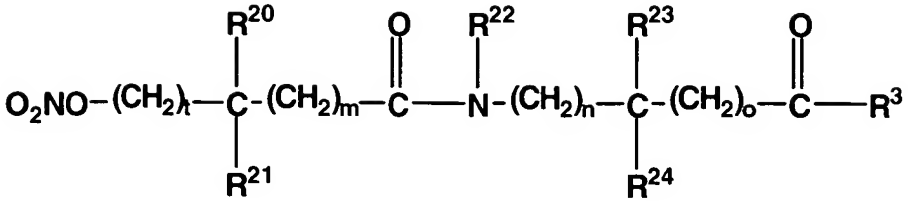
R^5 and $R^{5'}$ are each independently R^4, $R^{4'}$ hydrogen or lower alkyl;

R^2 and R^3, and $R^{2'}$ and $R^{3'}$, can be linked together to form an ester or an amide;

R^1 and R^2, and $R^{1'}$ and $R^{2'}$, can be linked together to form an alkylene bridge having 2 to 4 carbon atoms, an alkylene bridge having 2 to 3 carbon atoms and a sulfur atom, an alkylene bridge having 3 to 4 carbon atoms, which contains a double bond or an alkylene bridge, optionally substituted by hydroxyl, lower alkoxy, lower alkyl or di-lower-alkyl;

m, n, o, p, q, m', n', o', p' and q' are each independently integers from 0 to 10;

wherein the compound of Formula (II) is:



(II)

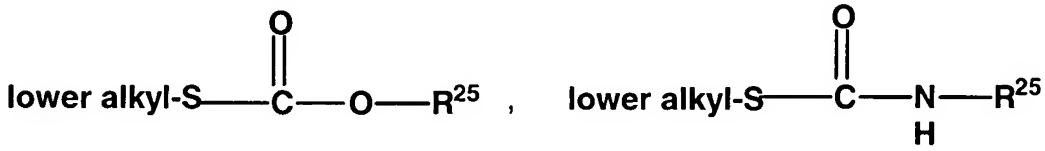
wherein:

R^{20} and R^{21} are each independently a hydrogen, an alkyl having 1 to 6 carbon atoms, a substituted lower alkyl in which the substituent is a halogen, groups defined by R^3 containing hydroxy, lower alkoxy, aryloxy, amino, lower alkylamino, acylamino, acyloxy, arylamino, mercapto, lower alkylthio or arylthio;

R^{22} is hydrogen or lower alkyl;

R^{23} is hydrogen, lower alkyl, phenyl, methoxy phenyl, phenyl-lower alkyl, methoxyphenyl-lower alkyl, hydroxyphenyl-lower alkyl, hydroxy-lower alkyl, alkoxy-lower alkyl, amino-lower alkyl, acylamino-lower alkyl, mercapto-lower alkyl or lower alkylthio-lower alkyl;

R^{24} is lower alkyl thiol, -SH, S-acyl compound of lower alkylthiol, preferably -S-acetyl, -S-propionyl, -S-butyryl, -S-isobutyryl, -S-capryl, -S-pivaloyl , -S-benzoyl;



and lower alkylthio-lower alkanoic acid and esters and amides thereof, and lower alkylthio-lower alkyl;

R^{25} is hydrogen and lower alkyl groups in which R^3 and R^{24} are bonded together and form part of a thiolactone group, groups in which R^3 and R^{23} are bonded together in the form of an ester or amide, groups in which R^{22} and R^{23} are bonded together in the form of an alkylene bridge with 2 to 4 carbon atoms, an alkylene bridge with 2 to 3 carbon atoms and a

sulfur atom, an alkylene bridge with 3 to 4 carbon atoms, which contains a double bond or an alkylene bridge as above, which can be substituted by one or more hydroxy, lower alkoxy, lower alkyl or di-lower alkyl groups; and

R^3, m, n, and o are as defined herein.

2. The method of claim 1, further comprising administering a pharmaceutically acceptable carrier.

3. The method of claim 1, further comprising administering at least one NSAID, COX-2 inhibitor, H_2 receptor antagonist, proton pump inhibitor, vasoactive agent, steroid, ß-agonist, anticholinergic, mast cell stabilizer, PDE inhibitor, taxane, rapamycin, tranilast, or mixture of two or more thereof.

4. The method of claim 1, wherein the compound of Formula (I) is:

N'-3-nitratopivaloyl-L-cysteinamide-glutathione mixed disulphide,

N'-3-nitratopivaloyl-L-cysteine ethyl ester-glutathione mixed disulphide;

N'-3-nitratopivaloyl-L-cysteine ethyl ester-N'-acetyl-L-cysteine mixed disulphide;

N-(3-nitratopivaloyl)-L-cysteine ethyl ester-D,L-penicillamine mixed disulphide;

2-acetylamino-3-(2-(2,2-dimethyl-3-nitrooxy-propionylamino)-2-ethoxycarbon ylethyl disulphanyl)-3-methylbutyric acid;

N,N'-di(3-nitratopivaloyl)-L-cystine;

N,N'-di(3-nitratopivaloyl)-D,L-homocystine;

N,N'-di(3-nitratopivaloyl)-L-cystine diethyl ester;

N,N'-di(3-nitratopivaloyl)-D,L-homocystine diethyl ester;

N,N'-di(3-nitratopivaloyl)-L-cystine di-tertiary-butyl ester;

N,N'-di(4-nitratomethylbenzoyl)-L-cystine dimethyl ester;

N,N'-di(3-nitratomethylbenzoyl)-L-cystine dimethyl ester;

N,N'-di(4-nitratomethylbenzoyl)-L-cystine-di(N,N'-butylamide);

N,N'-di(3-nitratomethylbenzoyl)-L-cystine-di(N,N'-butylamide);

N,N'-di(4-nitratomethylbenzoyl)-L-cystinediamide;

N,N'-di(3-nitratomethylbenzoyl)-L-cystinediamide;

N,N'-di(3-nitratopivaloyl)-L-penicillamine disulphidediamide;

N,N'-di(3-nitratopivaloyl)-L-cystinediamide;

N,N'-di(3-nitratopivaloyl)-L-cystine-di(N,N'-methylamide);

N,N'-di(3-nitratopivaloyl)-L-cystine-di(N,N'-butylamide);

N,N'-di(3-nitratopivaloyl)-L-cystine-di(N,N'-tertiary-butylamide);

N,N'-di(3-nitratopivaloyl)-L-cystine-dimorpholide;

N,N'-di(3-nitratopivaloyl)-L-cystinediisopropyl ester, or a pharmaceutically acceptable salts thereof.

5. The method of claim 1, wherein the compound of Formula (II) is

N-nitrato-pivaloyl-S-(N-acetyl-glycyl)-L-cysteine ethyl ester (compound SPM 5186);

N-nitrato-pivaloyl-S-(N-acetyl-alanyl)-L-cysteine ethyl ester (compound SPM 5185);

N-nitrato-pivaloyl-S-(N-acetyl-leucyl)-L-cysteine ethyl ester. N-(2-nitratoacetyl)-cysteine ethyl ester;

N-(2-nitratoacetyl)-S-acetyl-cysteine ethyl ester;

N-(2-nitratoacetyl)-S-propionyl-cysteine ethyl ester;

N-(2-nitratoacetyl)-S-pivaloyl-cysteine ethyl ester;

N-(2-nitratoacetyl)-methionine methyl ester;

N-(2-nitratopropionyl)-cysteine;

N-(2-nitratopropionyl)-cysteine ethyl ester;

N-(2-nitratopropionyl)-methionine ethyl ester;

N-(2-nitratobutyryl)-cysteine;

N-(2-nitratobutyryl)-cysteine ethyl ester;

N-(2-nitratobutyryl)-S-acetyl-cysteine ethyl ester;

N-(2-nitratobutyryl)-S-butyryl-cysteine ethyl ester;

N-(2-nitratobutyryl)-methionine ethyl ester;

N-(2-nitratoisobutyryl)-cysteine;

N-(2-nitratoisobutyryl)-cysteine ethyl ester;

N-(2-nitratoisobutyryl)-S-benzoyl-cysteine ethyl ester;

N-(2-nitratoisobutyryl)-S-acetyl-cysteine ethyl ester;

N-(2-nitratoisobutyryl)-S-pivaloyl-cysteine ethyl ester;

N-(2-nitratoisobutyryl)-methionine ethyl ester;

N-(3-nitratobutyryl)-cysteine;

N-(3-nitratobutyryl)-cysteine ethyl ester;

N-(3-nitratobutyryl)-S-acetyl-cysteine ethyl ester;

N-(3-nitratobutyryl)-S-propionyl-cysteine ethyl ester;

N-(3-nitratobutyryl)-methionine ethyl ester;

N-(3-nitratobutyryl)-homocysteine thiolactone;

N-(3-nitratopivaloyl)-cysteine;

N-(3-nitratopivaloyl)-cysteine ethyl ester;

N-(3-nitratopivaloyl)-cysteine ethyl ester-S-ethyl carbonate;

N-(3-nitratopivaloyl)-S-acetyl-cysteine ethyl ester;

N-(3-nitratopivaloyl)-S-propionyl-cysteine ethyl ester;

N-(3-nitratopivaloyl)-S-butyryl-cysteine ethyl ester;

N-(3-nitratopivaloyl)-S-isobutyryl-cysteine ethyl ester;

N-(3-nitratopivaloyl)-S-pivaloyl-cysteine ethyl ester;

N-(3-nitratopivaloyl)-S-benzoyl-cysteine ethyl ester;

N-(3-nitratopivaloyl)-methionine ethyl ester;

N-(3-nitratopivaloyl)-methionine;

N-(3-nitratopivaloyl)-homocysteine thiolactone;

N-(2-nitratohexanoyl)-cysteine ethyl ester;

N-(2-nitratohexanoyl)-S-propionyl-cysteine ethyl ester;

N-(3-nitratohexanoyl)-cysteine ethyl ester;

N-(3-nitratohexanoyl)-methionine methyl ester;

N-(12-nitratolauroyl)-cysteine;

N-(12-nitratolauroyl)-cysteine ethyl ester;

N-(12-nitratolauroyl)-S-acetyl-cysteine;

N-(12-nitratolauroyl)-S-pivaloyl-cysteine;

compound SPM 3672; compound SPM 6373; or a pharmaceutically acceptable salts thereof.